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Risk factors for recent transmission of *Mycobacterium tuberculosis*

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ABSTRACT: In recent decades, the decline of tuberculosis has stopped in Western Europe, mainly due to increased immigration from high-prevalence countries. The objective of the current study was to identify risk factors for developing tuberculosis following recent infection, in order to better target interventions.

Strains from 861 culture-positive cases, diagnosed in Norway in 1994–1999, were analysed by use of restriction fragment length polymorphism (RFLP). A cluster was defined as two or more isolates with identical RFLP patterns. Risk factors for being part of a cluster were identified by univariate and multivariate analysis.

A total of 134 patients were part of a cluster. These constituted 5% Asian-born, 18% Norwegian-born, 24% European-born and 29% African-born patients. Four independent risk factors for being part of a cluster were identified: being born in Norway, being of young age, being infected with an isoniazid-resistant strain and being infected with a multidrug-resistant strain.

Transmission of tuberculosis may be further reduced by improving case management, contact tracing, preventive treatment, screening of immigrants and access to health services for the foreign-born population.

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In recent decades, the decline of tuberculosis has stopped in Western Europe. This is mainly linked to increased immigration from countries with a high prevalence of tuberculosis, illustrating that tuberculosis is of growing concern globally. In Norway, the incidence of tuberculosis is among the lowest in Europe, five to seven cases per 100,000 inhabitants. While only 5% of the population in Norway was foreign-born in 2001, 74% of tuberculosis patients were reported to be from this group [1]. Tuberculosis services should, therefore, focus on such groups with the greatest risk of developing tuberculosis.

Generally, deoxyribonucleic acid (DNA) restriction fragment length polymorphism (RFLP) analysis of *Mycobacterium tuberculosis* applies the IS*6110* element as its probe. This is an internationally established method, well suited to study the epidemiology and transmission of tuberculosis [2]. Strains with identical IS*6110* RFLP patterns from different patients are assumed to represent cases of recent transmission.

The proportion of tuberculosis patients who are found to be part of a cluster varies considerably between different areas. In Norway, this proportion was 17% in the period 1994–1998 [3, 4], while much higher proportions (47–49%) were found in the Netherlands [5], Denmark [6], New York City, NY, USA [7] and the USA (sentinel surveillance study) [8]. Equally low levels were found in Zurich, Switzerland [9], and Vancouver, Canada [10], while the levels were intermediate (32–34%) in Hamburg, Germany [11], and western Canada [12]. The reasons for these differences have not been not well explained.

RFLP analysis has also been used to identify independent risk factors/predictors for being part of a cluster. This is widely interpreted as indicating recent infection [5, 9–11]. Risk factors have varied between studies and have included: drug abuse, alcoholism, homelessness, urban residence, male sex, young age, being foreign born, long-term residence in the country and pulmonary tuberculosis.

The objective of this study was to identify risk factors for acquiring tuberculosis following recent infection in a low-incidence country, in order to better target interventions.

Materials and methods

Study subjects

All cases reported to the National Tuberculosis Register in Norway in 1994–1999 were reviewed in this study. All cases of tuberculosis are required, by law, to be notified to this register. Clinicians give details about tuberculosis patients and laboratories report findings of tubercle bacilli. In addition, the pharmacy of Rikshospitalet University Hospital (Oslo, Norway) distributes all tuberculosis drugs in the country and, therefore, provides the National Tuberculosis Register with lists of patients to whom prescriptions are delivered. The notification is therefore considered to be quite complete [13].

A total of 25 microbiological laboratories, covering the whole country, isolated *M. tuberculosis* from patient samples. The strains of *M. tuberculosis* were collected at the Norwegian Institute of Public Health (Oslo, Norway), which functions as

a national reference laboratory for tuberculosis. The number of cases with culture confirmation was assessed, as well as the proportion of strains resistant to isoniazid and to both isoniazid and rifampin (multidrug resistance).

Study design

The study was a form of case-control design nested within the cohort of all cases of tuberculosis in whom isolates of *M. tuberculosis* were obtained. The study compared patients who were part of a cluster (cases) with patients who were not part of a cluster (controls, clustering being the dependent variable), with regard to various independent variables (risk factors): place of birth, sex, age, site of disease, resistance to isoniazid and multidrug resistance.

Methods

The strains collected at the Norwegian Institute of Public Health underwent RFLP analysis as described previously [4]. In brief, digested chromosomal DNA was hybridised to a probe targeted against the mobile IS*6110* element [14]. The RFLP patterns were compared by visual examination and computer-assisted analyses by use of the GelCompar version 4.1 software (Applied Maths, Kortrijk, Belgium). A cluster of isolates was defined as two or more isolates that exhibited 100% identical RFLP patterns. Cases caused by laboratory cross-contamination were excluded as explained previously [4]. Isolates with less than five copies of IS*6110* were excluded from this study because the genetic information was too limited to ascertain the identity of the strains.

Analysis

Place of birth has been found to be a major risk factor for tuberculosis and for being in a cluster. Therefore, the incidence of tuberculosis by place of birth from all the cases notified to the National Tuberculosis Register in 1994–1999 and the sum of the population on January 1 each year (provided by Statistics Norway, Oslo, Norway) was first calculated. The percentage of males, median age and proportion of pulmonary tuberculosis were calculated by place of birth.

The proportion of cases with less than five copies was calculated for each risk factor, since excluding cases with strains with less than five copies could be a confounder. For the patients included in RFLP analysis, the percentage clustered by age group and continent and the percentage clustered by resistance pattern and continent were presented separately.

Risk factors for being in a cluster were first assessed by univariate analysis, calculating odds ratios with 95% confidence intervals, and Fisher's exact test was used if the expected cell value was <5. The risk factors were: place of birth, male sex, age (in four groups), site of disease, resistance to isoniazid and multidrug resistance. Information on risk factors was taken from the notification forms in the National Tuberculosis Register. Median age was compared by the Mann-Whitney U-test. Multivariate logistic regression was then used in a model consisting of the five variables mentioned above to identify independent risk factors.

Results

Among the 1,411 cases of tuberculosis notified in Norway during the period 1994–1999, the overall notification rate was low (5.4 cases per 100,000 per year), but it was 18-times higher in the foreign-born than in the Norwegian-born population (table 1). The incidence varied considerably between continents: it was five-times higher in persons born in Europe, 29-times higher in those born in Asia and 92-times higher in those born in Africa, compared with those born in Norway. A few countries predominated: 79% of the European-born tuberculosis patients were from former Yugoslavia and 72% of the African-born from Somalia.

The majority of Norwegian-born and African-born patients were males, while there were more females among the European-born and Asian-born patients. The median age was 72 yrs among the Norwegian-born patients and 31 yrs among the foreign-born patients. African-born patients had the lowest median age of 27 yrs. Pulmonary cases represented 72% of Norwegian-born patients and 58% of the cases in the foreign-born population, with a large variation from <50% in patients born in Pakistan and Somalia to 92% in patients born in the former Yugoslavia (table 1).

The diagnosis was confirmed by culture in 67% of the cases

Table 1. – Notified cases of tuberculosis by place of birth, incidence, percentage of male, median age and pulmonary location

Place of birth	Total number of cases notified 1994–1999	Cases per 100,000 inhabitants	Male %	Median age yrs	Pulmonary site %
Norway	685	2.8	59	72	71
Foreign	726	49.2	51	31	55
Europe[#]	107	13.7	47	36	82
Asia[¶]	329	81.3	44	33	51
Africa[+]	272	258.3	62	27	50
Americas[§]	12	6.7			
Total[ƒ]	1411	5.4	55	45	63
Selected countries					
Somalia	197	839.4	57	26	44
Pakistan	122	169.1	47	35	41
Philippines	30	101.5	23	33	60
Thailand	14	89.9	7	28	79
Vietnam	58	89.9	43	33	52
Former Yugoslavia	84	77.5	46	36	85

[#]: Albania (four patients), Romania (three), UK (three) and 13 patients from 11 other countries; [¶]: India (29), Srilanka (21), Iraq (13), China (nine), Iran (eight), Turkey (six) and 19 patients from 14 other countries; [+]: Ethiopia (19), Morocco (15), the Gambia (six), Sudan (six), Uganda (six), Eritrea (four), Zambia (four) and 15 patients from 11 other countries; [§]: Peru (five) and seven patients from six other countries; [ƒ]: including one case from Oceania and five cases with unknown foreign country of birth.

Table 2. – Cases with culture confirmation, cases with susceptibility results, with strains with isoniazid and multidrug resistance, and number of cases with result from restriction fragment length polymorphism (RFLP) analysis, by place of birth

Place of birth	All cases with culture confirmation n (%)	Susceptibility			All cases with RFLP analysis n (%)
		Cases n	Isoniazid resistance %	Multidrug resistance %	
Norway	429 (63)	399	2.3	0.5	396 (92)
Foreign	510 (70)	491	11.0	1.8	465 (91)
Europe	63 (59)	61	6.6	1.6	63 (100)
Asia	235 (71)	227	8.4	0.4	210 (89)
Africa	202 (74)	195	15.9	3.6	183 (91)
Americas	7 (58)	7	0.0	0.0	7 (100)
Total[#]	939 (67)	890	7.1	1.2	861 (92)
Selected countries					
Somalia	154 (78)	152	18.4	3.9	139 (90)
Pakistan	87 (71)	82	8.5	0	72 (83)
Philippines	20 (67)	20	10.0	0	17 (85)
Thailand	12 (86)	12	8.3	0	12 (100)
Vietnam	45 (78)	44	9.1	0	45 (100)
Former Yugoslavia	49 (58)	48	4.2	2.1	47 (96)

[#]: including three cases with unknown foreign country of birth.

and this value was higher in the foreign-born population (table 2). Resistance to isoniazid was more frequent in foreign-born patients, with proportions highest in patients born in Africa. Multidrug resistance was low in Norwegian- and Asian-born patients, while higher in African- and European-born patients (table 2).

RFLP results from *M. tuberculosis* cultures were available from 905 patients in the National Reference Laboratory. These were matched, by date of birth and name, with the National Tuberculosis Register. A total of 904 patients were found in the National Tuberculosis Register. The last patient had not been notified, but was included in the study after data was collected from the local health authorities. Of the 905 patients studied, 44 were excluded: a total of 33 cases were false-positive, caused by laboratory cross contamination, nine were registered outside the study period and two were registered twice during the study period. A total of 861 patients entered the study. The study population included 92% of the tuberculosis cases with culture confirmation reported during 1994–1999.

A total of 11.2% of the cases were excluded because the strains carried less than five copies of IS*6110* and this value was significantly higher in foreign-born (18.4% (95% confidence interval 14.8–22.0)) than in Norwegian-born patients (2.8% (1.1–4.4)). The proportion was 1.6% (0–4.7) in patients born in Europe, 24.2% (18.3–30.1) in patients born in Asia (it was especially high in patients born in Vietnam) and 18.0% (12.3–23.7) in patients born in Africa (table 3). The patients included in the study did not differ significantly from all the patients notified during this period with regards to the assessed risk factors (data not shown).

Among the isolates that carried more than four copies of IS*6110*, 18% were part of a cluster. While there was no significant difference in clustering by unadjusted analysis between Norwegian- and foreign-born patients as a group, the proportion varied greatly by continent of birth. A total of 29% of the African-born patients, 24% of European-born, 17% of Norwegian-born and 5% of Asian-born patients were infected with clustered isolates. By country, patients born in Somalia had a higher proportion in clusters than Norwegian-born patients, while those from Vietnam, Pakistan and Thailand/Philippines had a lower proportion (table 3). By multivariate analysis, however, being born in Norway was a significant risk factor compared with being born in Europe, Asia or Africa.

Young age was an independent risk factor for being in a cluster. Median age for patients with clustered isolates was significantly lower than in those infected with unique isolates: in all patients 35 and 54 yrs, respectively ($p>0.001$); in Norwegian-born patients 56 and 75 yrs, respectively ($p<0.001$); and in foreign-born patients 25 and 32 yrs, respectively ($p=0.001$). The proportion of clustered isolates declined with increasing age of the patients. It was lower in foreign-born patients than in Norwegian-born patients in all age groups (fig. 1).

Being infected with a strain that was resistant to isoniazid or was multidrug resistant were independent risk factors (table 3). There was a strong association between multidrug-resistant tuberculosis and being born in Somalia. Of a total of 10 new patients diagnosed with multidrug-resistant tuberculosis in Norway in 1994–1999, seven were Somali in origin (one born in Asia) infected with identical *M. tuberculosis* isolates. Two patients of Norwegian origin and one from Bosnia were infected with unique multidrug-resistant strains. In total, 44 patients had strains resistant to isoniazid but not to rifampicin. Patients born in Somalia represented 20 of all these cases and 11 of the 16 cases in the cluster (table 4).

Discussion

Being part of a cluster often suggests that *M. tuberculosis* was recently transmitted to the patient. The current study identified four independent risk factors for being part of a cluster. These included being born in Norway, being of young age and being infected with a strain that was resistant to isoniazid or was multidrug resistant. It was demonstrated that Norway has a very low incidence of tuberculosis and that a low proportion of the tuberculosis cases were clustered.

Being born in Norway came out as a risk factor compared with being born abroad. This was in spite of the much lower incidence of tuberculosis (creating fewer sources of infection) and the higher median age found in the native Norwegian population. In order to be part of a cluster, two or more persons need to have been infected from the same source at one time in the recent or remote past and to be diagnosed with the disease during the period of the study. Since most cases in Norwegian-born patients are caused by reactivation of remote infection, being part of a cluster is believed to be often caused by a coincidental reactivation in two or more cases with a

Table 3. – Tuberculosis patients with strains with five or more copies of IS*6110* and patients in cluster, with unadjusted and adjusted odds ratios (OR)

Vaiable/category	Patients with ⩾5 bands		Of whom in cluster		Unadjusted univariate OR (95% CI)	Adjusted multivariate OR (95% CI)[#]
	n	%	n	%		
All cases	765	89	134	18		
Place of birth						
Norway	385	97	68	18	1.0	1.0
All foreign[¶]	380	82	66	17	1.0 (0.7–1.3)	0.2 (0.1–0.4)[+]
Norway	385	97	68	18	1.0	1.0
Europe	62	98	15	24	1.5 (0.8–2.8)	0.4 (0.2–0.9)
Asia	160	76	8	5	0.2 (0.1–0.5)	0.1 (0.0–0.2)
Africa	150	82	43	29	1.9 (1.2–2.9)	0.4 (0.2–0.7)
Country of birth						
Norway	385	97	68	18	1.0	
Former Yugoslavia	47	100	13	27	1.5 (0.9–2.6)	
Somalia	111	80	35	32	1.8 (1.3–2.5)	
Vietnam	24	53	0	0	p<0.03[§]	
Pakistan	65	90	4	6	0.4 (0.1–0.9)	
Thailand/Philippines	23	79	0	0	p<0.03[§]	
Sex						
Male	414	88	80	19	1.3 (0.9–1.9)	1.1 (0.7–1.7)
Female	351	89	54	15	1.0	1.0
Age						
0–24 yrs	137	89	41	30	1.0	1.0
25–44 yrs	225	79	49	22	0.7 (0.4–1.1)	0.7 (0.4–1.1)
45–64 yrs	105	91	15	14	0.4 (0.2–0.5)	0.2 (0.1–0.5)
65+ yrs	298	97	29	10	0.3 (0.1–0.4)	0.1 (0.0–0.2)
Site of disease						
Pulmonary	507	92	102	19	1.8 (1.2–2.7)	1.6 (1.0–2.6)
Extrapulmonary	258	84	32	15	1.0	1.0
Resistance to isoniazid and rifampicin[§]						
Sensitive to both	703	89	108	16	1.0	1.0
Resistant to isoniazid, sensitive to rifampicin	44	90	16	44	3.1(1.6–6.0)	3.1 (1.4–6.6)
Multidrug resistant	10	100	8	73	22.0 (4.6–105.2)	16.4 (3.2–83.3)

CI: confidence interval. [#]: adjusted for continent of birth, sex, age group, location and resistance; [¶]: including six cases from the Americas and two with unknown foreign place of birth; [+]: adjusted for Norwegian *versus* non-Norwegian place of birth instead of continent; [§]: Fisher's exact test used if expected value was <5; [f]: eight cases without result of susceptibility testing.

strain that was prevalent in the past and not by recent transmission.

While the proportion of Norwegian-born patients in the cluster was the same as foreign-born patients overall (17%), by multivariate analysis it was significantly higher in Norwegian-born patients. This is partly explained by the difference in age. Young age was an expected risk factor that has also been found in other studies [5, 11]. A young person has a lower probability than an older person of being infected previously, due to the substantial decline in the risk of being infected within Norway. In young persons, new transmission will more often lead to new infection.

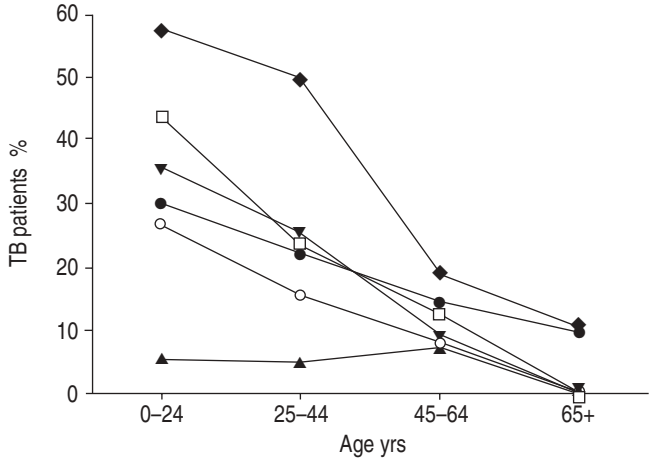

Fig. 1. – Percentage of tuberculosis (TB) patients in cluster by place of birth and age. ◆: Norway; □: Europe; ▼: Asia; ●: Africa; ○: foreign born; ▲: total.

One reason why the proportion of foreign-born patients in the cluster was relatively low in spite of the high incidence of tuberculosis could be that most of the patients were probably infected before arrival to Norway. Other patients infected with the same strain of *M. tuberculosis* may still reside in the countries where the patients had been infected, while other members of the clusters with Norwegian-born patients will be detected by the Norwegian health services. Another indication that recent transmission contributes little to tuberculosis is the observation that transmission between foreign-born patients and Norwegian-born persons or between different ethnic groups occurs rarely, since clusters seldom include persons of different ethnic groups [4]. The same was also noted in Denmark [15].

Surprisingly, resistance to isoniazid and multidrug resistance were found to be risk factors for being part of a cluster, as resistant strains have been suggested to be less virulent than sensitive strains [5, 16, 17] and being infected with an isoniazid-resistant strain was found to be a risk factor for not being part of a cluster in the non-Dutch population in the Netherlands [5]. Nevertheless, at least with the multidrug-resistant strains, the increased duration of being a case might

Table 4. – Tuberculosis cases in cluster by resistance pattern and place of birth

Place of birth	Sensitive to isoniazid and rifampicin		Resistant to isoniazid and sensitive to rifampicin		Multidrug resistant	
	Total n	In cluster n (% of total)	Total n	In cluster n (% of total)	Total n	In cluster n (% of total)
Norway	372	63 (17)	6	3 (50)	2	0 (0)
Europe	58	14 (24)	2	0 (0)	1	1 (100)
Asia	144	6 (4)	14	1 (7)	1	1 (100)
Africa	121	25 (21)	22	12 (55)	6	6 (100)
Total	703[#]	108 (15)	44	16 (36)	10	8 (80)

Only patients with strains with five or more IS*6110* copies in restriction fragment length polymorphism analysis are included. [#]: including six cases from the Americas and two with unknown foreign place of birth.

have increased the probability of transmitting infection. Moreover, drug resistance may be an indication of poor quality of treatment, either due to errors of the health services (failing to observe swallowing of medication) or to improper prescription or irregular taking of medications, again possibly prolonging the period of infectiousness. The major outbreak identified by IS*6110* RFLP in Norway during the study period was due to a drug-resistant and multidrug-resistant strain of *M. tuberculosis*. This strain was mainly isolated from Somali refugees in Oslo and is believed to influence the present results [18]. Seven of 10 multidrug-resistant cases of tuberculosis were found in this group.

Some risk factors for transmission of tuberculosis identified in other studies [5, 9] are not yet important in Norway. No nosocomial outbreaks have been reported. Few patients have dual human immunodeficiency virus (HIV) and tuberculosis infection, as most of the Norwegian-born tuberculosis cases are too old to be HIV infected and most foreign-born persons are from countries with low levels of HIV infection. Although *i.v.* drug abuse is a serious problem in Norway, no major outbreaks of tuberculosis have yet occurred among addicts. Regular chest radiography screening has been carried out in this group in collaboration with needle exchange programmes and has probably contributed to preventing outbreaks. The number of homeless people is relatively low and chest radiography screening is also being carried out in this group in hostels. These factors may explain the striking difference in clustering between Norway and Denmark, where these risk factors are more frequent and several outbreaks have occurred [6].

This study included 92% of all culture-positive patients in the whole country over a 6-yr period. All patients with RFLP results were found in the National Tuberculosis Register. An important constraint was that 11% of the isolates carried less than five copies of the IS*6110* element and were therefore excluded from the analysis. Moreover, although the material was drawn from a whole country over an extended period, the low percentage of cases in cluster limits the statistical power of the study. A few clusters may influence the findings disproportionately. Data on clusters should be complemented with information about epidemiological links, since clustering may also be caused by a link in the past and where re-activation of old infections occur at about the same time.

The current study indicates that contact tracing needs to be strengthened in the Norwegian-born part of the population in order to reduce diagnostic delay. It also appears that preventive treatment (*i.e.* isoniazid for 6 months, or isoniazid and rifampicin for 3 months for infected persons before they develop disease) for Norwegian-born patients would have a limited effect on the transmission of tuberculosis in this country. Even though the 68 Norwegian-born patients that were part of a cluster were significantly younger than those who were not part of a cluster, only 11 were $\leqslant$35 yrs and would be obvious candidates for preventive treatment. Twenty of the clustered Norwegian-born patients were between 35–50 yrs. This age group could be considered for preventive treatment, while the remaining 37 patients were too old to make preventive treatment recommendable because of the side-effects of isoniazid.

Tuberculosis in Norway is now mainly an "imported" disease, but there are two different patterns of disease among immigrants. Among some groups, mainly patients from Asian countries who have been in Norway for many years, there was very little clustering, while the notification rate was relatively high. Most Pakistan-born persons came to Norway as economic migrants in the 1970s and most Vietnamese-born persons arrived as refugees in the 1980s. Many females from the Philippines and Thailand have arrived because of work or marriage to Norwegian males. Thus, Asian immigrants have arrived from different countries through many decades and constitute a heterogeneous group. Some may also have been infected during recent visits to their country of origin [19]. For these reasons it was not surprising that a low degree of transmission was found in this group. It should be remembered, however, that many Asian-born cases, especially from Vietnam, were excluded from this study, as they had strains that carried less than five copies of IS*6110*. It was suggested that preventive treatment could have a great impact on the notification rate in the Asian-born patients. Tuberculin testing should be offered after prolonged visits to countries of origin with a high prevalence of tuberculosis.

In other groups (notably those from Africa), both notification rates and the proportion of clustered cases were high. In this group especially, clustering was also associated with drug resistance. Most of the African-born patients had recently arrived to Norway as refugees from Somalia. The incidence of tuberculosis in Somalia is among the highest in the world with a high transmission of tuberculosis [15, 16, 18]. Such disease may possibly have been exacerbated by prolonged periods in transit centres and refugee camps. It is likely that many persons who arrived in Norway previously had close connections in Somalia or such camps. Many may, therefore, have been infected with the same strain prior to arrival to Norway. However, by assessing epidemiological links in Norway, it was clear that some of these were infected after arrival to Norway [18]. The proportion of patients with clustered isolates may remain high even after several years in a new country, such as observed in Denmark [20]. This may be caused by continued transmission but also due to re-activation of infection acquired before arrival.

The current study indicates that the tuberculosis control programme targeted for this group of patients needs improvement in several areas, including case management, with emphasis on direct observation of treatment, rapid detection of rifampicin resistance, improved infection control policies, improved contact investigation and more broadly

offered preventive therapy. These measures are also emphasised in the new Norwegian guidelines on tuberculosis prevention and control [21]. The access to health services needs to be strengthened for the foreign-born population with symptoms of tuberculosis. Most cases appear months and years after arrival to Norway.

Finally, the present study indicates that services need to be focused on specific groups for the long-term reduction of tuberculosis in low-prevalence countries. The risk of becoming infected with *Mycobacterium tuberculosis* and developing disease varies tremendously between population groups. Since most cases among the foreign born are caused by infection before arrival, support to strengthen tuberculosis-control programmes in high-prevalence countries is also needed.

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